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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/307,223	05/07/1999	JUDITH A. VARNER	6627-PA11	4575

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Kamrin T. Macknight
MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, CA 94105

EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	17

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/307,223	Applicant(s) Varner et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 5, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-5, 9-14, 19, 20, 55-72, 75, and 80-120* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 9-14, 19, 20, 55-72, 75, and 80-120* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Response filed March 5, 2002 (Paper No. 16) to the Office Action of November 16, 2001 (Paper No. 15) is acknowledged and has been entered. Claims 1-5, 9-14, 19-20, 55-72, 75, 80-120 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. It is noted that Applicant has cited numerous instances of case-law in the response. In situations where Applicant has not disclosed either the relevance of the case law to the instant rejections or whether or not the case law is drawn to an analogous art, the case-law has not been considered.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

4. Claim 2 remains rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 15, Section 4, Page 2.

Applicant (a) reiterates previous arguments drawn to the recitation of preferred mathematical ranges for binding and raises the question as to whether those skilled in the art would understand what is claimed, (b) Applicant states that the Woods Declaration is submitted and that the Woods Declaration demonstrates that the term "substantially is understood by one skilled in the art wherein Dr. Wood's concludes that it is his understanding that the term "substantially" in recited in claim 2 means that the agent's interference with the specific binding of alpha 5 beta 1 integrin is at least two-fold greater than the interference of the agent with the specific binding of another integrin to its cognatel ligand. Thus because the term

"substantially" is clear to Dr. Woods who is one skilled in the art, this term is definite.

The arguments have been considered but have not been found persuasive because (a') of the reasons previously set forth, (b') although a Curriculum Vitae of Dr. Virgil Woods was received, no Declaration was received with this response, thus, it is not possible to either consider or evaluate the Declaration. However, it is reiterated, for the reasons previously set forth, that claim 2 is indefinite because the term "substantially"is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. If Dr. Woods understands the scope of the claims after discussion with Applicant, this understanding does not provide clarification for the public, at large, for the reasons previously set forth. Applicant's arguments have not been found persuasive and the rejection is maintained.

5. Claims 80-86, 90-96 and 110-116 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 15, Section 10, page 16.

Applicant argues that the specification provides adequate support as evidenced by the enclosed Declaration by Dr. Woods wherein Dr. Woods, who is skilled in the art, concluded that the inventor contemplated this desired property with any agent and in view of Dr. Woods's Declaration the specification conveys to the artisan that the inventor was in possession of the recited binding ranges with respect to the recited agent.

The argument has been considered but has not been found persuasive because as previously set forth, no Declaration was received with this response, thus, it is not possible to either consider or evaluate the Declaration. However, even were the Declaration, as described, to be submitted and considered it is not relevant whether or not the inventor was in possession at the time the invention was made since it appears that the inventor chose not to mention this broadly claimed limitation in the specification or claims as originally filed. Applicant is invited to point to page and line of the specification wherein support can be found for the broadly claimed limitation. Applicant's arguments have not been found persuasive and the rejection is maintained.

6. Claims 86, 96 and 116 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 15, Section 11, pages 16-17.

Applicant reiterates arguments drawn to the Woods Declaration. The arguments are not persuasive for the reasons set forth previously . Applicant is invited to point to support for the newly added limitations in the specification and claims as originally filed. Applicant's arguments have not been found persuasive and the rejection is maintained.

7. Claims 80-120 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in paper No. 15, Section 12, pages 17-20.

Applicant argues that (a) claims 1-5, 9-14, 19-20, 55-72 and 75 are enabled and thus all claims dependent upon those claims are enabled, (b) selective binding is irrelevant because the term is not recited in any of the claims and since specific binding is defined by the specification without any regard to quantitation, the

meaning of the term is clear and applicants can be their own lexicographers, (c) the specification is enabling because it teaches screening methods to determine levels of angiogenesis and so does the prior art, (d) even if agents with less than 100-fold greater affinity to alpha 5 beta 1 than to another integrin did not result in the recited reduction of angiogenesis this would not negate enablement , (e) successful therapy is irrelevant because it is not recited in the claims and what is recited is that the agent reduces angiogenesis and this is enabled by the above-discussed routine methods and the variables referred to by the Examiner are immaterial, (f) Kim et al rebuts the Examiner's contention of non-enablement by further demonstrating that the Specification's routine methods may be used to determine the level of angiogenesis in a tissue in response to administration of an agent, (g) Pasqualini et al rebut the Examiner's contention that variables associated with the agent point to non-enablement because the same variables are implicated in Pasqualini et al's use of sFN to inhibit cancer.

The arguments have been considered but have not been found persuasive because (a') the instant rejection is not drawn to any of the broadly written claims 1-5, 9-14, 19-20, 5-72 and 75. MPEP 2164.08(b) specifically teaches that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled, thus although nonworking embodiments can be included in broadly written claims, when these nonworking embodiments are specifically claimed they are not enabled and are properly rejected under 35 USC 112, first paragraph and for the reasons previously set forth, the rejected claims are not enabled, (b') Applicant is correct, specific binding is defined by the

specification and as recited in claim 1 is appropriately drawn to the association of a ligand to the integrin. However, although the redefinition of "specific binding" appears to be inappropriate, the issues remain the same when drawn to the "agent" since the specification clearly teaches that fibronectin is selective for the alpha 5 beta 1 integrin and the claims are drawn to a method of reducing or inhibiting angiogenesis in a tissue. Although it is clear that the rejected claims do not recite "selective binding" it is also clear that no one of skill in the art would believe it more likely than not that the invention would function as claimed if the "agent" bound only specifically as defined by the specification. In the absence of selectivity for the broadly claimed "agent", for the reasons previously set forth, the invention is not enabled. The fold-binding limitations, given what was known in the art, are not sufficient to confer selective binding on the claimed "agent" for the reasons previously set forth and therefore the claims as currently constituted are not enabled, (c') and (f') the ability to screen does not overcome the lack of enablement drawn to the "fold-binding" for the reasons previously set forth since the claims are specifically drawn to a method of using agents with those fold-binding parameters. Given what was known in the art, no one of skill would believe it more likely than not that the invention would function as claimed, (d') the specification does not teach how to use inoperative embodiments, (e') inherent in the reduction of angiogenesis in a tissue is the therapy of that tissue, the invention is not enabled for the reasons set forth previously and above and the variables referred to by the Examiner are pertinent and critical to the enablement of the invention as claimed, (g') Pasqualini et al enable sFN but not Applicant's broadly claimed "agents".

Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 102

8. Claims 1-5, 9-13, 55-66, 68-69, 71-72, 75 and 80-120 remain rejected under 35 USC 102(e) for the reasons previously set forth in Paper No. 15, Section 5, pages 3-6 and in Paper No. 9, Section 8, pages 5-8 drawn to the rejection of claims 1-5, 9-13, 55-66, 68-69, 71-72, 75.

Applicant (a) reiterates previous arguments drawn to "each and every element" and the lack of express disclosure, (b) argues that because Examiner has not established anticipation and therefore Applicant need not show a thing. The arguments have been considered but have not been found persuasive (a') for the reasons previously set forth, (b') in the absence of objective evidence, anticipation has been established for the reasons previously set forth.

Applicant further argues that (c) Examiner does not provide evidence of inherency (d) the proper application of "inherency is shown by *Glaxo Inc. v. Novopharm Ltd*, (e) applicant reiterates arguments that not one but several alternative pathways could be the mechanism of sFN action thus inherency is not established, (f) applicant requests a nexus between sFN and FN, (g) Applicant does not admit on the record that sFN interferes with the binding of 5 different receptors on endothelial cells, including alpha 5 beta 1 to their respective ligands, but rather Applicant provided evidence which shows that sFN bindings to 5 different receptors which are different from alpha 5 beta 1, (g) Examiner misunderstands the law of inherency and reiterates previous arguments, (h)(i) Examiner does not understand

the thrust of scientific evidence that in that there is a functional difference between the biological effects of sFN and FN, (h)(ii) Applicant requests clarification of what "limitations" she is referring to". The arguments have been considered but have not been found persuasive because (c') Examiner clearly stated that the invention appears to be the same as the prior art invention, given that the sFN is simply a multimeric form of the claimed FN. Further, Examiner clearly stated the the Office does not have facilities for examining and comparing applicant's method with the prior art method in order to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed method is functionally different than those taught by the prior art and to establish patentable differences. In the absence of objective evidence demonstrating that sFN does not act in the same manner as FN on the claimed receptor, the rejection is maintained, (d') the case law disclosed is not drawn to an art analogous to an *in vivo* method of reducing or inhibiting angiogenesis, (e') the arguments are not persuasive for the reasons previously set forth, (f') Applicant is referred to Paper No. 15, page 7, (g') a review of the previous response revealed that the actual statement was that fibronectin is known to bind to five receptors other than alpha 5 beta 1 and that it is probable that when Pasqualini et al suggests that sFN may inhibit angiogenesis, that this inhibition may result from sFN's interference with the binding of any one or more of the six receptors to their respective ligands. Examiner apologizes for any misunderstanding, (g') for the reasons previously set forth, Examiner is not relying

on the law of inherency and the reiterated arguments are not persuasive for the reasons previously set forth, (h')(i) sFN is a multimeric form of FN which is ligand claimed and which would clearly, for the reasons previously set forth, meets the claimed limitations of the "agent", although sFN exhibits functional characteristics not seen in FN, this does not obviate the fact that sFN is a multimeric form of FN, that the alpha 5 Beta 1 receptor is the FN receptor and that sFN would be expected not only to bind to that receptor with higher avidity and affinity than any other receptor but also that its binding would interfere with the binding of FN. Finally, the cited reference, using sFN, is clearly drawn to the reduction of angiogenesis (h)(ii) Applicant is referred to Paper No. 15, Section 5(c)(iv), page 5.

Applicant submits objective evidence and argues that (i) Yi et al proposes mechanisms of action for sFN which do not include alpha 5 beta integrin, (j) and states that the mechanism of the antiangiogenic activity of antiangiogenic substances that are derived from modifying ECM such as FN is unknown and cites p. 624, para bridging cols 1 and 2, (k) Yi advances two hypotheses for the mechanism of action of sFN, neither of which involves interference with alpha 5 beta 1 and those hypotheses stand for the proposition that Pasqualini et al's sFN reduces metastasis by impacting tumor cells, not endothelial cells, (l) the prior art demonstrates that Pasqualini et al's HT29 cells do not express alpha 5, beta 1 integrin and thus the conjected inhibition of angiogenesis cannot possibly be mediated by sFN's interference with the binding of alpha 5 beta 1 integrin to a ligand. The arguments have been considered but have not been found persuasive because (i') and (k') the reference does not teach that sFN does not bind to alpha 5 beta 1 integrin or that it

would not interfere with the binding of a ligand, (j') a review of the paragraph bridging cols 1 and 2 does not reveal the cited information, (k') in the absence of objective evidence, the Yi hypotheses do not provide support for Applicant's argument, (l') the relevance of the argument is unclear since Pasqualini clearly teaches a method of treating neovascularization with the multimeric form of FN.

Applicant submits objective evidence and further argues that (m) Morla et al teach that superfibronectin is a functionally distinct form of fibronectin and that sFN binds to multiple receptors and are superadhesive on cells which **may be** (emphasis added) due to sFN binding to a family of receptors not related to integrins, (n) Examiner has not shown how to exclude the probability that sFN inhibits angiogenesis by interfering with these non-integrin receptors, (o) Applicant reiterates previous arguments drawn to experimental differences demonstrated between the sFN and the claimed "agent" on cell migration. The arguments have been considered but have not been found persuasive because (m') the functional distinction of superfibronectin appears to be its superadhesiveness, there is no teaching that sFN binds to receptors other than integrins, there is no teaching that sFN does not bind to alpha 5 beta 1 integrin or that it would not interfere with the binding of a ligand to alpha 5 beta 1 integrin or that it would not function as instantly claimed, (n') the claimed invention appears to be the same as the prior art invention, Applicant has not submitted objective evidence that establishes that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method, (o') the arguments are not persuasive for the

reasons previously set forth. Applicant's arguments have not been found persuasive and the rejection is maintained.

9. Claims 1-3, 9-13, 55, 57-63, 65, 66, 71-72, 75 and 80-97, 100-106, 108-117, 119-120 remain rejected under 35 USC 102(e) for the reasons previously set forth in Paper No. 15, Section 6, pages 6-8.

Applicant argues that (a) Ex parte Novitski is not analogous to the instant fact pattern because, unlike the instant fact pattern wherein there are mechanisms for sFN to act which do not implicate alpha 5 beta 1 integrin, Novitski is drawn to a claim which does not have alternate protection paths, (b)(i) Ruoslahti et al rebuts inherency in Pasqualini et al since no nexus is provided between FN and sFN, (ii) Ruoslahti et al demonstrate that peptides which inhibit binding to alpha 5 beta 1 are associated with inhibiting attachment of tumor cells to fibronectin and since Examiner defines sFN as a "peptide" Rusolahti et al teaches away from the claimed invention, (c) Applicant reiterates arguments drawn to HT29 cells that do not express alpha 5 beta 1 integrin, effects of sFN are not necessarily mediated via alpha beta 1, sFN suppresses cell migration on both fibronectin and collagen.

The arguments have been considered but has not been found persuasive because (a') the possible alternate pathways do not negate the inherency argument, since Applicant has not shown that the invention is materially, functionally or structurally different than that taught by the prior art and it is noted that Applicant has admitted on the record that fibronectin is known to bind to five receptors other than alpha 5 beta 1. Given that sFN is a multimeric form of fibronectin, it would be expected that sFN would specifically interfere with the binding of FN to its ligand,

alpha 5 beta 1 as claimed, (b')(I') the nexus has been provided and is well known in the art, (ii') peptides clearly come in all sizes and the peptides recited in Rusolaht et al are clearly different than sFN since they consist of from about 5-10 residues, (c') the arguments are not persuasive for the reasons previously set forth. Applicant's arguments have not been found persuasive and the rejection is maintained.

10. Claims 80-106, 108-117, 119-120 remain rejected under 35 USC 102(e) for the reasons previously set forth in Paper No. 15, Section 7, pages 8-9.

Applicant incorporates her arguments and evidence in connection with overcoming the previous rejections.

The arguments have been considered but have not been found persuasive for the reasons set forth previously and above.

Claim Rejections - 35 USC § 103

11. Claims 1-5, 9-13, 19-20, 55-72, 75, 80-106, 108-117, 119-120 remain rejected under 35 USC 103 for the reasons previously set forth in Paper No. 15, Section 8, pages 9-13.

Applicant argues that (a) Examiner has not established that the combined references disclose or suggest the limitations of the claims, (b) Applicant argues the references individually, (c) Applicant reiterates arguments drawn to motivation and the association of angiogenesis with alpha 5 beta 1 integrin expression, (d) examiner uses impermissible hindsight in the rejection of the claims, (e) Applicant reiterates arguments drawn to alleged inherency, (f) Applicant reiterates arguments drawn to eye drops and states that none of the claims recite administration of the agent using eye drops, (g) Applicant clarifies the prior response wherein he stated that the

disclosure of Thorpe was irrelevant to selected claims because they do not recite cytotoxin-linked agents and states that because Examiner referred Applicant to claims 19 and 20 which do recite the claimed agents and did not further comment, that the validity of the argument is conceded, (h) Applicant states that Pasqualini et al's disclosure of cytotoxin-linked agents adds nothing to the reference's inadequate motivation for reducing or inhibiting angiogenesis and the Examiner did not respond to this argument, accordingly it stands unrebutted, (i) Applicant clarifies the prior response wherein he stated that the disclosure of intratumoral injection was irrelevant to selected claims because they do not recite intratumoral injection and states that because Examiner referred Applicant to claim 67 which does recite the claimed limitation and did not further comment, that the validity of the argument is conceded, (j) Applicant states, as previously argued, that the alleged motivation to inject the agent fails to supplement the insufficient motivation for reducing or inhibiting angiogenesis and the Examiner did not respond to this argument, accordingly it stands unrebutted, (k) Applicant reiterates arguments drawn to a reasonable expectation of success and states again that the involvement of alpha 5 beta 1 integrin with angiogenesis was unknown prior to the instant specification, (l) applicant reiterates arguments drawn to improper inherency, (m) Applicant reiterates arguments and teachings of Yi et al and Morla et al, Varner et al and Ruoslahti et al and states that sFN is functionally different from agents which interfere with specific binding of alpha 5 beta 1 to a ligand, (n) Applicant reiterates arguments drawn to a reasonable expectation of success and points again to the references cited above.

The arguments have been considered but have not been found persuasive because (a') for the reasons of record, the combined references disclose or suggest the limitations of the claims, the instant rejection was made to further address the limitations drawn to a cytotoxin, a chemotherapeutic drug, administration into a neoplasm and administration of the agent by eye drops, all of which are obvious in light of the combined prior art; (b') Applicant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981), (c') the combined references provide motivation for the reasons previously set forth, (d') in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Clearly, it was well known in the art, as taught by Pasqualini et al, that an "agent" sFN was known to be a ligand for alpha 5 beta 1

integrin and was specifically shown to inhibit angiogenesis. Pasqualini et al in combination with the other cited references makes obvious the claimed invention. Contrary to Applicant's assertion, the references teach not only the suggestion but also the means and motivation to successfully make a method of reducing or inhibiting angiogenesis in a tissue as claimed. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981), (e') the arguments are not persuasive for the reasons previously set forth, Examiner does not rely upon inherency, Applicant is referred to Paper No. 15, Section 5, page 5, item (b') and Section 7, pages 8-9, (f') the arguments are not persuasive for the reasons previously set forth, further, Applicant is referred to claim 70 which is specifically drawn to eye drops, (g') the validity of the argument was not conceded and no comment concerning those claims was required because Applicant did not distinctly and specifically point out the supposed errors in the rejections of claims 19 and 20, (h') the argument drawn to inadequate motivation for reducing or inhibiting angiogenesis was and has been rebutted throughout Examiner's responses to arguments, the motivation for producing cytotoxin-linked agents was clearly disclosed and since Applicant did not address the issue of producing cytotoxin-linked agents and did not specifically point out the supposed errors in the obviousness rejections drawn to cytotoxin-linked agents, Examiner did not reiterate

the responses previously made, (') the validity of the argument was not conceded and no comment concerning claim 67 was required because Applicant did not distinctly and specifically point out the supposed errors in the rejections of claim 67, (j') the argument drawn to inadequate motivation for reducing or inhibiting angiogenesis was and has been rebutted throughout Examiner's responses to arguments, the motivation for intratumoral administration was clearly disclosed and since Applicant did not address the issue of intratumoral administration and did not specifically point out the supposed errors in the obviousness rejections drawn to cytotoxin-linked agents, Examiner did not reiterate the responses previously made, (k') for the reasons previously set forth, the arguments are not persuasive and further, the method is obvious for the reasons set forth previously and above, (l') the argument was not persuasive for the reasons set forth previously and above, (m') the arguments are not persuasive for the reasons set forth above, further, although the Yi et al and Morla et al references describe some differences in the functionality of sFN and FN, neither reference presents objective evidence demonstrating that the prior art invention is not the same as the claimed invention and further, no showing has been made that sFN is functionally different from agents which interfere with specific binding of alpha 5 beta 1 to a ligand, that is, no showing has been made that sFN does not interfere with specific binding of alpha 5 beta 1 to a ligand, (n') there is a reasonable expectation of success for the reasons set forth previously and above, and for the reasons set forth above, the cited references are not persuasive. Applicant's arguments have not been found persuasive and the rejection is maintained.

12. Claims 1-5, 9-14, 19-20, 55-72, 75, 80-120 remain rejected under 35 USC 103 for the reasons previously set forth in Paper No. 15, Section 8, pages 9-13.

Applicant argues (a) the references individually, (b) that the association of alpha 5, beta 1 with angiogenesis was unknown prior to the instant specification and therefore there is no motivation to combine, (c) that Examiner does not establish a reasonable expectation of success, (d) that Ruoslahti et al teaches away from the claimed invention.

The argument has been considered but has not been found persuasive because (a') Applicant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981), (b') and (c') the argument drawn to motivation has been previously made and responded to, the invention is obvious for the reasons previously set forth and motivation with a reasonable expectation of success has been previously presented, (d') for the reasons previously set forth, given the information in the art and in the combined references, the claimed invention is obvious over US Patent No. 5,922,676 as evidenced by WO95/14714. Applicant's arguments have not been found persuasive and the rejection is maintained.

12. All other objections and rejections recited in Paper No. 15 are withdrawn

13. No claims allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
May 8, 2002